The value of primary colposcopy in genitourinary medicine—a six year review

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Abstract

***Objective*—To evaluate the effectiveness of primary colposcopy in the genitourinary medicine setting by comparing the cervical cytology and punch biopsy results for women identified as having an abnormal cervical transformation zone.**

***Method*—A retrospective audit of six years' findings in primary colposcopy was carried out. The punch biopsy findings of 1338 women were compared with their last cervical cytology results. A small sample of biopsies were subjected to in situ hybridisation for human papilloma virus types 6, 11, 16, 18 and cytomegalovirus.**

***Results*—The tabulated results demonstrated the variability between histology and cytology. This was explored with reference to other studies. The viral typing showed the dominance of low oncogenic risk human papilloma virus types.**

***Conclusion*—The findings are discussed against the overall concept of sexual health. Primary colposcopy facilitates empowerment of the patient and her partner through the opportunity for demonstration and explanation of disease processes and options for management. Experience and expertise gathered in six years of primary colposcopy confirm the value of primary colposcopy not only in improved diagnosis and management but also in teaching, audit and research.**

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Introduction

The basic premise of cervical screening is that changes identified on Papanicolaou smear can be defined on colposcopic examination and categorised either by punch, cone[1] or loop diathermy biopsy. Many recent papers have questioned the correlation between these three diagnostic processes.[2] The vast majority of studies acknowledge that as yet we do not know the natural progression of cervical intraepithelial neoplasia (CIN),[3] although it is widely accepted that CIN III will progress to invasive disease in some one-third of untreated cases.[4]

The difficulty with cervical screening is that we are trying to put dynamic biological systems into categories and it is not always easy to do so as CIN is a spectrum of disease with overlapping areas.

In 1981 a local charity made a donation which enabled this department to purchase its first Leisegang colposcope. Donation and investment of that size at that time seemed unusual in genitourinary medicine and, therefore, we were motivated to make maximum use of the instrument. This led to magnifying the cervix in every new female patient as part of an attempt to acquire experience, knowledge and understanding of both acute chlamydial disease of the cervix and, in particular, to try to identify the reported follicular cervicitis of chronic chlamydial disease (acknowledged by most histopathologists to be a follicular lymphoid inflammatory process on cervical biopsy).[5] The prevalence of genital chlamydial infection in this district peaked shortly after this time and appears to have gradually declined.[6]

The department inherited at Doncaster in 1980 demanded the development of small sub-waiting areas which have always seemed to be comfortable for the patients and have recently been very considerably improved as a result of Monks Report implementations.[7] The ethos and ambience of the clinic is considered important in primary colposcopy. Prospective pilot studies, together with patient satisfaction questionnaires confirm that the investigation is not only acceptable, but it also improves the doctor-patient relationship, patient understanding and, of particular interest, decreases the fail-to-attend rate.[8]

The basic clinical suite which is reproduced five times to make the total clinic, is that of a discrete doctor/patient/partner consulting area, a female examination room, each of which has a colposcope and video unit en suite and a male examination room immediately adjacent. The design is intended to promote the attendance and management of couples as well as individuals. There is no segregation of sexes within the different sub-waiting environments.

The increased availability of colposcopy during 1981–1985 had been reinforced by training in diagnostic colposcopy at Professor Sharp's Gynaecology Unit at the Northern General Hospital in Sheffield. The previous experience of routinely magnifying the cervix, followed by availability of instruments and later training in diagnosis and management of CIN, immediately raised the question as to whether there was a role for primary colposcopy within what was perceived to be a high risk group.

The concept of high risk groups within genitourinary medicine has continued to be an area of brisk debate, but Clare Wilkinson's

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views published in the *British Journal of General Practice*[9] may well be worthy of further attention. Dr Wilkinson has argued that more precise targeting of high risk groups might offer a means of enhancing preventive efficiency. Based on a wide review of world literature Dr Wilkinson proposed four independent risk factors for CIN: the woman's educational level, current smoking habit, years of oral contraceptive use and, number of sexual partners.

Whilst the debate continues we remain convinced that we do indeed see some patients who are at high risk[10] and almost certainly always have done.

An initial review of the results of primary colposcopy and the comparison of biopsy and last smear result was completed in 1989, this was extended and the study period now covers six and a half years, from March 1986 to October 1992.

Patients, method and materials

The diagnoses of 1338 women undergoing primary or low threshold colposcopy who were found to have an abnormal transformation zone and who consented to subsequent punch biopsy were audited. Biopsies were not performed if there were aceto-white areas ascending into the endocervical canal; these patients were referred for gynaecological assessment.

The biopsy findings were compared with the latest cervical cytology result. The smear and biopsy were frequently performed on the same occasion, the majority of the remainder were taken within three to six months of colposcopy, but on occasion cytology ante-dated colposcopy by up to twelve months. Where the results reported more than one category or a point between two categories, such as "cytology: viral + mild dyskaryosis or histology: CIN I to CIN II," the higher grade was used.

Results

Of the women who underwent primary or low threshold colposcopy, 1338 were found to have an abnormal transformation zone. All those audited had consented to subsequent biopsy. The highest grade of change in biopsy fundings was compared with the highest grade of smear result (table 1).

The majority of abnormalities (772 out of 1338, 57·7%) showed koilocytosis, multinucleation or dyskeratosis; thus there was evidence of viral change. It is important to note that 309 (23·1%) of these women had normal histology in biopsy specimens.

Cervical intra-epithelial neoplasia (CIN) of all grades was identified in 165 of these women, which gives an average CIN rate of 12·3% between 1986 and 1992. The rate appeared to be steadily increasing, from 6% in 1986 and just below 10% in 1989; however, other factors may have affected this.

Of 1338 women with abnormal colposcopy results, 92 (6·9%) had biopsies showing cervicitis. There was no severely dyskaryotic cytology associated with any of the cervicitis biopsies.

The biopsy findings were compared with the last available cytology results (table 1), and the negative biopsies correlated by and large with either negative smears or with very low grade cytological changes.

Very few of the inflammatory biopsy specimens were associated with inflammatory cytology, but this was anticipated, as earlier experience allowed us to identify colposcopic features of acute inflammatory disease in the cervix, and colpo-biopsy would then be postponed until antimicrobial therapy had been achieved.

Where viral changes were reported in the biopsy specimens it was interesting to note that half of the smears failed to identify koilocytosis. The Cytology Department has now refined the cytological diagnosis of HPV, which requires koilocytosis, dyskeratosis and multinucleation before being entered on the cytology report form. Histological diagnosis is a different process, hence some apparent discrepancy is inevitable. About a third (252 out of 772, 32·6%) did identify viral changes cytologically and histopathologically, but amongst the viral changes 78 (10·1%) had a smear suggesting dyskaryosis, the majority of which were mildly dyskaryotic.

Of the CIN group the apparent false negative rate on cytology was 24·2% (40 out of 165). Therefore it appeared that both cytology and punch biopsy had a possible false negative rate of approximating to 1 in 4. Different outcomes may have become apparent if loop diathermy or cone biopsy had been used.

Applying the National Co-ordinating Network current clinical management Guide-

Table 1 Comparison of cervical smear result and punch biopsy findings in 1338 women where primary colposcopy suggested an abnormal cervical transformation zone

Smears	*Biopsies NAD*	*Viral*	*Cervicitis*	*CIN*	*Total*
Negative	183	382	52	40	657
Viral	59	252	20	39	370
Borderline	18	38	5	12	73
Inflammatory	12	22	7	5	46
Mild	31	63	6	47	147
Moderate	6	11	2	13	32
Severe	0	4	0	9	13
Total	309	772	92	165	1338

NAD: No abnormality detected. CIN: Cervical intra-epithelial neoplasia.

Table 2 Comparison of cervical smear result and 165 punch biopsy findings for grades of CIN from 1338 women where primary colposcopy suggested an abnormal cervical transformation zone

Smears	*Biopsies CIN I*	*CIN II*	*CIN III*	*Total*
Negative	25	11	4	40
Viral	25	8	6	39
Borderline	7	3	2	12
Inflammatory	3	0	2	5
Mild	27	15	5	47
Moderate	6	6	1	13
Severe	1	5	3	9
Total	94	48	23	165

lines[11] to the highest grade CIN (table 2), over half (12 out of 23) of the small number of CIN III yield would not have been referred for colposcopy, about a third (7 out of 23) would be referred for further cytology in six months time and less than 1 in 5 with histological evidence of CIN (4 out of 23) would be referred for colposcopy. This caused considerable concern, but the literature increasingly refers to the observation that small area CIN of high grade has as yet an unknown potential for progression[12] and some authors consider colposcopic abnormalities exceeding 2 quadrants of the cervix important in defining potential progression.[2]

There appears to be little doubt that human warts virus can cause bizarre nuclear changes in addition to koilocytosis, and the interpretation of both cytology and histology is confounded by the effects of HPV.[8] Histology findings from our study showed that CIN was often a mixed lesion, showing CIN plus HPV in two-thirds of reported cases; only one-third showed pure CIN.

In this audit the CIN II and CIN III group comprise 71 out of 1338 patients (5·3%), of whom 15 (21·1%) had a current negative smear. A wide range of changes was identified in those with non-normal smears, with dyskaryosis suggested in 35 (49·3%). The current National Co-ordinating Network Guidelines for Clinical Practice and Programme Management[11] state unequivocally that CIN II and CIN III should be treated once diagnosed. Therefore it caused concern that apparently only half of the major grade cervical disease had been identified by the last cervical smear.

Amanda Herbert *et al*[2] recognised that owing to the subjective nature of both cytological and histological assessment intra- and inter-observer variations are inevitable. We recognise that in primary genitourinary colposcopy this discrepancy may be expanded by the presence of HPV against the background of small cervical lesion size. Dr Herbert and colleagues recommended, having regard for the nature of the tests, that a discrepancy between the cytology and histology was significant when there was a difference between them of at least two degrees. We therefore looked at the maximal inter-observer variation, that is, high grade lesions with negative last cervical cytology. This comprised a group of 15 with only 4 CIN IIIs. An audit (not fully blinded review) led to all Papanicolaou smears and biopsies being reviewed in the same laboratory by the same consultant pathologist. On review 12 of the 15 slides had evidence of dyskaryosis, two did not have a smear reflecting the lesion and one was thought to be an inadequate smear.

Other workers have reported more worrying variance. Sriskandabalan *et al*[3] looked at 428 women with negative cervical smears colposcoped because of genital warts using punch biopsy and found 146 CIN cases reporting five with invasive carcinomas.

There was a final small review of the primary colposcopy/CIN cases by a member of our Histopathology Department using in situ hybridisation techniques to look at HPV and CMV.[14] The aim of the project was to investigate the hypothesis that the presence of HPV in the female genital tract increases the risk of acquisition of other sexually transmitted diseases by looking at CMV, and to evaluate the independent association of each virus with CIN. This study involved 24 biopsies from genitourinary patients being probed for HPV6, 11, 16, 18 and CMV using a standard non-isotopic in situ hybridisation protocol.

The CMV probe was used somewhat reluctantly as an Epstein Barr virus (EBV) probe was not available commercially. The original hypothesis was that EBV causes changes similar to koilocytosis in oral hairy leucoplakia[15] and also that more than one pathogen is commonly identified in genitourinary medicine.

Seventy-five CIN biopsies from the genitourinary primary colposcopy study were reread "blind". Twenty-four cases were selected at random; these were all studied with in situ hybridisation. They included all grades of CIN and all had histological evidence of HPV.

Eight negative controls were also studied; these were cervical biopsies from eight female patients with no evidence of CIN or HPV change. None of the viruses under investigation was identified in the control group.

Of the 24 CINs with viral change, eight (33%) were positive for HPV6, five (21%) were positive for HPV11, six (25%) were positive for HPV16 (perhaps the most interesting group for it may well be that this is the real risk area to be identified), and none for HPV18 or CMV. None were positive for more than two types of HPV and in each case where more than one type of HPV was present, only one type gave a signal in any one cell. There were two biopsy specimens showing a positive signal to viral Type 6 and 11 and one interesting specimen showing both the low risk HPV11 signal and high risk HPV16 signal[14] (table 3).

Although we expected to see positive signals in cells that were not koilocytosed, this was not found in this study. This may be due to the sample being taken from women with an abnormal cervical transformation zone and not from women in earlier stages of disease.

When these results were tabulated it appeared quite convincing that viral types 6 and 11 were associated with low grade lesions and type 16 was associated with higher grade

Table 3 Results of in situ hybridisation using probes for HPV types 6, 11, 16, 18 and CMV by grade of CIN at histological diagnosis for a sample of 24 biopsies

Probes	*CIN I*	*CIN II*	*CIN III*	*Total*
HPV6	8	0	0	8
HPV11	4	1	0	5
HPV16	0	5	1	6
HPV18	0	0	0	0
CMV	0	0	0	0
Total + ve results	12	6	1	19
Positive cases	10	5	1	16
Negative cases	5	2	1	8
Total cases	15	7	2	24

Two CIN I biopsies were positive for HPV6 and HPV11. One CIN II biopsy was positive for HPV11 and HPV16.

lesions. There was no positive signal to type 18 and this is in accord with much of the UK literature.[16]

Discussion and conclusion

It has been asked in the context of increasing awareness of responsibility for cost effective management "is primary colposcopy cost effective?" It has not been fully costed or evaluated, but there are many reasons to expect that this process is financially expedient, not least is the fact that high cost capital equipment is in use in virtually every clinic with a majority of new female cases.

We have now gone from unstained magnification of the cervix looking for infectious disease to assessing for possible CIN *during the same consultation* by cervical staining. However, this step was taken at a time when it was assumed that the degree of cytological dyskaryosis correlated approximately with the degree of CIN.

A six year audit of primary colposcopy has led to a questioning of that assumption. The current hypothesis is that endeavours to prevent CIN and cervical cancer can be combined simultaneously with endeavours to prevent the sequelae of ascending genitourinary infection in women. Indeed both diseases may co-exist simultaneously or at different times in the same individual. Perhaps a fundamental role of primary colposcopy is to measure the sensitivity of cervical cytology. The specificity is difficult.

The current NCN recommendations for clinical practice and programme management now include the following:- *"In young women HPV may be one of a multiplicity of sexually transmitted diseases present simultaneously and referral to a genitourinary medicine clinic should be considered."*[11]

The six year audit of primary colposcopy has also led to the following observations regarding benefits to patients, benefits to the community and additional value in teaching and research.

The procedure benefits both patient and partner where there is increased speed, accuracy and understanding of the diagnosis. There is empowerment of the patient through explanation and involvement in the decision making. The process has reinforced counselling and health education. Our patients have reported to us that it reduces fear and embarrassment, and decreases stigmatisation and humiliation. We have a "no secrets" approach which again, our patients tell us they value.

All of these enhance the patient-doctor relationship, as do those values of primary colposcopy which are based on the clinician or carer. These include early detection of CIN and increased understanding of the limits of the range of investigations available. Psychological studies to date reporting very high degrees of stress immediately before colposcopy appear to all be based on this separation of opportunistic or routine cervical cytology examination from the process of colposcopy at a later date.

We have had to expand laterally our concepts of cervical health and disease experience. We have increased the discrimination in diagnosis of multiple concomitant cervical disease and we have decreased the fail-to-attend follow-up rate in both prospective studies showing statistical significance[8] and in patient satisfaction questionnaires. Possibly this is through provision of the "one-stop" specialist service.

We believe there are community benefits. There is an increased awareness and understanding within our community that cervical health is one part of sexual health. There is an increased uptake of cervical screening services and the well-informed community contributes to counselling.

General practitioners have advised us that their referral of patients for genitourinary screening and colposcopy where there is a risk of both infectious and pre-malignant disease is facilitated by this approach.

Areas of additional value are in teaching and research. Teaching includes teaching the patient and learning for the colposcopist. Medical training at all levels is enhanced. At Doncaster there is particular emphasis on general practice and junior doctors work through the GP Vocational Training Scheme (VTS). A full-time VTS Senior House Officer post is attached to the unit. Specialist nurse training is also enhanced across the board.

In larger teaching units the concept of closed loop video systems cabled to a central teaching unit to minimise patient intrusion enhances teaching without adding to anxieties or distress experienced by the individual patient, although this has not yet been established locally.

The process facilitates research which may no longer always be cytologically led. All clinical, epidemiological, microbial and cellular biological areas of research and audit can be considered. Prospective studies looking at the inter-relationships between these groups are now in progress.

Finally a major contribution is one of quality control. We are left with the opinion that the availability of primary colposcopy increases the quality of cytology and histology and acts as a quality measure for the colposcopists themselves.

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